5:00

HEPARIN ENHANCES THE SYNERGISM BETWEEN PLATELET TXA2 SYNTHASE INHIBITION/RECEPTOR BLOCKADE (RIDOGREL) AND TISSUE PLASMINOGEN ACTIVATOR IN LYSING CANINE CORONARY THROMBI

Andre Van de Water, Raymond Xhonneux, Fred De Clerck, James T. Willerson, Janssen Research Foundation, Beerse, Belgium and The University of Texas Medical School and Texas Heart Institute, Houston, TX

Occlusive platelet-rich thrombi induced by intraluminal anodal stimulation of left anterior descending (LAD) coronary arteries in anesthetized, open-chest dogs were lysed with tissue plasminogen activator (rt-PA) (80 ug/kg intravenously + 4 ug/kg/min, 25 min after occlusion) with additionally (15 min before rt-PA): 1) solvent (S; n=5); 2) ridogrel, a combined thromboxane synthase inhibitor and receptor antagonist, (R; 5 mg/kg iv + 5 mg/kg/h; n = 5); heparin (H; 200 U/kg 2 x iv; n = 6); and 4) heparin + ridogrel (n = 6). Time to reperfusion (S = 81; R = 65; H = 65; H + R = 24.5 min*# median; P <0.05 *vs S; #vs H), rt-PA consumed prior to reperfusion (S = 404; R = 340; H = 340; H + R = 178 ug/kg, p<0.05 vs H), incidence of reocclusion within 120 min (S = 100%; R = 100%; H = 66%; H + R = 16.6%), time to reocclusion (S = 37; R = 29; H = 75.5; H + R = > 120 min*) and eventual thrombus mass (S = 49; R = 37; H = 7.5; H + R = 0 mg*#) were most affected by the heparin-ridogrel combination. These data demonstrate that the combination of ridogrel and heparin enhances the thrombolytic efficacy of rt-PA in this experimental model.

5:15

HEPARIN ENHANCES THROMBOLYSIS WITH rt-PA

Jozef S Mruk, James H Chesebro, Mark WI Webster, Pierre Zoldhelyi, Diane E Grill, Valentin Fuster, Mayo Clinic, Rochester, MN.

The coagulation cascade with thrombin generation is activated by thrombolysis. We compared the lytic effect (incidence of and time to reperfusion, residual thrombus by autologous ^{111}In-platelet deposition) of rt-PA plus high-dose heparin (100 U/kg, then 100 U/kg/hr IV) with that of rt-PA alone in a porcine carotid model of platelet-rich, occlusive arterial thrombosis, created by balloon dilatation followed by atherectomy. rt-PA was administered as 0.3 mg/kg bolus, 3 mg/kg over 90 min, then 1 mg/kg over 120 min. rt-PA plus heparin prolonged the activated partial thromboplastin time (APTT) 5.3±0.6 x basal, and was associated with major bleeding in 1 pig. ^{111}In-labeled platelet deposition (per cm^2 of carotid artery) was measured after sacrifice at 210 min in all animals.

	rt-PA	rt-PA+heparin
No. reperfused/total pigs	2/6	6/7
Time to reperfusion, min	90,120	10,80,80,120,180,210*
Platelet deposition, x10^6/cm^2	123±23	47±15

* mean 113 min

Considerable mural thrombus remained in the artery after 210 min of therapy following successful reperfusion with heparin plus rt-PA. In this model, thrombin inhibition with hirudin markedly enhanced thrombolysis with rt-PA (7/7 reperfused at 10-50 min [mean 33 min], APTT 2.4±0.1 x basal, ^{111}In-platelet deposition 13±3 x 10^6/cm^2).

High-dose heparin enhances thrombolysis with rt-PA, but is less effective than specific thrombin inhibition with hirudin.

Monday, March 4, 1991
4:00PM–5:30PM, Room 215, East Concourse
Histology of Restenosis: Clues to Pathogenesis?

4:00

RESTENOSIS DEVELOPS IN FOUR STAGES: SERIAL HISTOLOGIC STUDIES IN A CORONARY INJURY MODEL

Robert S. Schwartz, William D. Edwards, Joseph G. Murphy, Allan R. Camrud, David R. Holmes. Mayo Clinic and Foundation, Rochester, Minnesota, 55905.

Restenosis following PTCA remains a major, unsolved clinical problem. This may result in part from lack of knowledge regarding basic pathophysiologic processes. To better understand how restenotic lesions develop, a proliferative porcine coronary injury model using oversized metallic coils was studied at varying times following deep coronary arterial injury.

A total of 35 coronary artery lesions (L) in 20 pigs (P) were examined microscopically following sacrifice at 6 hours (8L, 4P), 3-4 days (6L, 3P), 7 days (7L, 4P), 13-14 days (4L,3P), and 28-30 days (10L, 6P). Four stages were identified in the development of proliferative, obstructive lesions. Stage I (6 hours) was characterized by a large, space occupying platelet-fibrin thrombus at the injury site. By 4 days (Stage II) the thrombus consisted of extensive fibrin clumps admixed with numerous erythrocytes, few intact platelets, and early endothelialization on the luminal surface. Stage III (7-14 days) was characterized by monocyte and lymphocyte infiltration, and by early ingrowth of medial smooth muscle cells (SMC). SMC mitoses were most prevalent at this time. In stage IV (14-28 days), SMC migration from the media formed a cap over the luminal side of the mass. Progressive downward growth of this cap resulted in the obstructive cellular lesion identical to that observed in human restenosis.

If similar reparative processes cause human restenosis, solutions to the restenosis problem may lie in the interruption of one or more of these stages.

4:15

ULTRASTRUCTURE OF HUMAN CORONARY AND PERIPHERAL ATHEROMATOUS PLAQUES REMOVED BY PERCUTANEOUS ATHERECTOMY

Gerhard Bauriedel, Ingeborg Schinko, Ulrich Windstetter, Ulrich Welsch, Berthold Höfling, University of Munich, W. Germany

Ultrastructural study of diseased coronary and peripheral arteries may help to understand more about plaque formation. 15 specimens from 8 coronary lesions and 81 from 20 femoral lesions were obtained by percutaneous atherectomy. Ultrastructure of primary stenoses from both approaches was compared by transmission electron microscopic evaluation. Coronary plaques showed abundant extracellular matrix (ECM) with poor cellularity. Smooth muscle cells were of elongated shape with large nuclei, narrow cytoplasmic borders and extended processes. Metabolically active cellular organelles were seen only infrequently. ECM consisted of numerous collagen fibers with scattered matrix granules, lipid droplets and adjacent cholesterol clefts. Peripheral lesions were characterized by less ECM, an increased number of cells with high secretory activity and a larger cytoplasma/nucleus ratio. In cell culture studies with explanted tissue specimens, cellular outgrowth was seen to occur significantly ($p<0.02$) earlier from peripheral than from coronary plaques (8.3 ± 0.7 versus 14.8 ± 2.5 days, x ± SD).

Conclusions: In contrast to our previous results from restenotic lesions, primary plaques were characterized by large ECM regions and poor cellularity, more so in coronary than in peripheral plaques. This local balance may contribute to morphology and activity of human plaque formation.

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